Collective Expert Report

Tobacco
Understand dependence in order to act

Summary and recommendations

INSERM

Institut National de la santé et de la recherche médicale

(National Institute for health and Medical Research)

This document presents the summary and recommendations of the expert group convened by Inserm through the collective expert evaluation procedure to answer the questions raised by the Interministerial Mission to Combat Drugs and Drug Addiction (Mission interministérielle de lutte contre la drogue et la toxicomanie, Mildt) concerning tobacco dependence .

It is based on the scientific information available as at the last six months of 2003. The document base for this expert evaluation consisted of approximately 1,000 articles and documents.

The Inserm Collective Expert Evaluation Centre co-ordinated this collective work with the Department for Facilitation and Scientific Partnership (Département animation et partenariat scientifique, Daps) to instruct the dossier and with the documentation service of the Department for Scientific Information and Communication (Département de l'information scientifique et de la communication, Disc) for the literature search.

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Foreword

According to the World Health Organisation (WHO), smoking is currently responsible for almost 5 million deaths per year throughout the world. Combating smoking has become a public health priority, justifying initiatives taken on an international scale such as "Pour un monde sans tabac" ("For a tobacco free world"). The framework agreement proposed by the WHO and adopted in May 2003 by 47 states invites countries to take measures which are recognised to be effective and to include these in a legislative setting (increases in price and taxes, banning advertising, prohibition of smoking in the workplace and public places, education and sensitisation campaigns, prohibition of sales to minors, etc).

In 2003 the Tobacco Control Country Profiles report (TCCP) which brings together data from 196 countries, stressed the very considerable increase in smoking in developing countries. Whilst approximately 50% of deaths currently occur in wealthy countries, 70% will be in developing countries between now and 2020. The prevalence of smoking in men is approximately 35% in developped countries, 50% in developing countries and more than 60% in China. If smoking follows its current trend, it will be responsible for 1 billion deaths during the 21st century. One billion people are currently dependent on smoking.

According to the EROPP 2002[1] survey, almost 12 million people in France in the 18 to 75 years age band are regular smokers, i.e. they smoke at least one cigarette per day. Smoking is recognised as being the leading avoidable cause of death. The most recent data indicate that smoking is responsible for 60,000 deaths each year. The prevalence of smoking in youth of 18 to 25 years old, including all those who state that they smoke even only from time to time, is almost 50%. These findings fully justify the French priority policy committed to combating smoking, as recommended on an international scale by the WHO.

The Interministerial Mission to Combat Drugs and Drug Addiction (Mildt) asked Inserm, through the collective expert evaluation procedure, to obtain the most recent scientifically valid data on the mechanisms of establishment of smoking dependence and the measures to counter it on an individual and community scale. Improved understanding of dependence and its determining factors should help to better define prevention policies, particularly in young people, and to improve the medical and psychological assistance given to smokers through advances in knowledge.

The expert group brought together for this work structured its thinking around the following questions :

What is the prevalence of smoking and tobacco dependence according to national and international studies? What are the results of longitudinal studies on the trajectory of smokers (initiation, experimentation, dependence, abstinence, relapses, lifelong abstinence)? What are the methods by which dependence is initiated and maintained and the interactions between tobacco dependence and other psychoactive substances?

What are the individual risk factors involved in tobacco dependence (genetic vulnerability, personality traits, psychiatric co-morbidities etc.)?

What are available data on the genes involved in tobacco dependence? Is there a common genetic vulnerability between certain psychiatric disorders (mood disorders, anxiety disorders, etc.) and tobacco dependence?

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[1] Survey on representations, opinions and perceptions of psychotropic agents, from the Observatoire français des drogues et des toxicomanies (OFCT) (French Monitoring Center for drugs and drug addiction).

What is the impact of cigarette smoke exposure during the foetal life and the development of dependence? What is the influence of the family and social environment on acquisition of smoking dependence?

What pharmacological data are available on nicotine and other compounds in tobacco implicated in tobacco dependence?

What are the mechanisms of action of nicotine and other contituents of tobacco or tobacco smoke on the central nervous system? What are the different neurotransmitter pathways implicated in nicotine dependence? What are the data provided by brain imaging? What neurosensory effects of nicotine or other compounds from tobacco are believed to be involved in tobacco dependence?

What information is provided by animal studies on tobacco/nicotine dependent behaviour and nicotine withdrawal?

How should be tobacco dependence diagnosed and treated? What are the current treatments and how effective they are? What are the new therapeutic approaches to help smokers quit smoking?

More than 1,000 articles were selected from international literature databases. The experts presented a critical analysis and a review of published international work on the different aspects of tobacco dependence during 9 working sessions, organised between the month of November 2002 and October 2003. From the validated knowledge the experts proposed recommendations for the prevention and management of smoking and highlighted the benefit of developing multi-disciplinary research to fill the many gaps identified during their analysis. Several communications provided further knowledge on the effects of nicotine, individual and social determinants of tobacco dependence and behavioural aspects of smoking cessation.

Summary

There are approximately 14 million smokers amongst the 18–75 year old population in France: nearly 12 million of these are regular smokers, i.e. they smoke at least one cigarette per day. Thirty-three per cent of men and twenty-six per cent of women are regular smokers. Use of tobacco is particularly common before the age of 35 years old and falls regularly thereafter with age.

Among young people up to the age of 18 years old, the percentage of smokers increases considerably. Sixty per cent of young children have smoked at least once in their lives at the age of 14; at the age of 18 this percentage exceeds 80%. Eight per cent of 14 years olds are regular smokers compared to 40% of 18 years olds. These figures are identical in boys and girls, whereas smoking is commoner in men than in women at all ages in adults. The difference between men and women increases with age as older women belong to generations in which smoking rates in women were lower. Boys and girls now begin to smoke at almost the same age (13.4 years old and 13.6 years old on average according to the Escapad survey 2000-2002[2]). This is also the case for adults under 35 years old whereas in older people women started later than men. However, more women than men stop smoking at a young age. In the population of regular smokers, the number of cigarettes smoked increases rapidly with age, reaching a maximum among the 40–50 years old. Quantitatively, men smoke a higher number of cigarettes than women.

As for use of other psychoactive substances, smoking is maintained and reinforced by dependence. Identification of tobacco dependence is based on clinical diagnostic criteria which are difficult to use in general population surveys and the available data come from a very small number of studies performed in the United States. As an indication, in a population in which 75% of people are or have been occasional or regular smokers, the main American study found a lifetime prevalence of tobacco/nicotine dependence in 24% of the entire population, -30% of all those who had smoked at some time in their lives and 50% of those who smoked regularly. Nicotine dependence is more common among heavy smokers and among young adults. Many smokers state that they wish to stop, although only a minority envisage doing so in the near future.
Among those who actually try to stop smoking, relapses occur frequently and result in multiple attempts to stop. Periods of abstinence are mostly short and approximately a quarter of these people manage to stop for at least one year.

Dependence on any psychoactive substance is a chronic disorder, characterised by a loss of control over its use, by a compulsive desire to consum it and a relative inability to go without it.

Tobacco smoke contains thousands of compounds, many of which may contribute to the establishment or maintenance of tobacco dependence. Of these compounds, nicotine is the constituent of tobacco which is most incriminated for its addictive potential (probably also because it is the most studied to date). However, in contrast to what one might think, the mechanisms through which nicotine or other components of tobacco or tobacco smoke

[2] Enquête par autoquestionnaire sur la santé et les consommations lors de l'appel de préparation à la défense (Self-completed questionnaire on health and consumption of psychoactive substances of all 18 years old during the call for preparation of the national defence).

induce dependence are still little understood. This fully justifies all ongoing evidence-based research.

The smoker adapts his/her method of smoking to obtain the amount of nicotine – and other substances – which he/she needs

The chemical composition of tobacco is very complex. It may be analyzed from the fresh or dried plant and from the tobacco and its additives in the cigarette. However, when the chemistry of tobacco is examined in the context of dependence, it is the analysis of what the smoker is exposed to which is important, and therefore the chemistry of cigarette smoke which we need to consider.

Data on cigarette smoke come from studies performed with the smoking machine, under clearly defined conditions. The smoking test is used to determine the amounts of tar, nicotine, and carbon monoxide obtained under standardized conditions, which are shown on cigarette packets by application of the European Directive relative to the labelling of tobacco products. Because smokers smoke according to their individual and specific way, the product labelling does not inform about the amount of substance a smoker inhales.

Of the different substances present in tobacco (more than 3,000) we do not know for certain which are liable to account for its addictive properties. For these substances to play a role in tobacco dependence, the smoker must be exposed to them at a sufficient concentration. Tobacco smoke can be defined as a dynamic moving aerosol formed from a vapour (or gaseous) phase and a particulate phase.

To our current knowledge, nicotine appears to be the main component to explain the addictive properties of tobacco. The amount of nicotine absorbed depends very much on the manner of smoking (whether or not the smoke is inhaled, volume and frequency of puffs, depth of inhalation etc.). It also depends on the type of tobacco consumed. Most cigarettes available on the market contain between 5 and 10 mg of nicotine and, according to the standardized smoking machine, the smoked cigarette yields around 1 mg of nicotine, indicating that the smoker may inhale approximately 1 mg of nicotine for each cigarette smoked. However, each smoker adapts his/her method of smoking in order to obtain the amount of nicotine (and/or other substances) which he/she needs (we refer to self-titration) and as a result the concept of the "mild" or "ultra-mild" cigarette, of lower yield, appears to be a misnomer, the reason why the European Union is, from now on, prohibiting these names.

Beta-carbolines (alkaloids) such as harmane and norharmane (10 to 20 μg) are found in tobacco smoke and have inhibitory properties on monoamine oxidases (MAO), involved in the degradation of monoamines such as dopamine. These could therefore play an important role in tobacco dependence. In addition, acetaldehyde and formaldehyde present in cigarette smoke may be responsible for the in vivo synthesis of beta-carbolines in smokers.

A few additives present in cigarettes (menthol, ammoniacal additives, flavouring agents) have been studied for their possible participation in tobacco dependence. Menthol has not been excluded as a contributor to the dependence through its action on the absorption or metabolism of nicotine in Afro-American population of smokers who preferentially to smoke mentholated cigarettes.

The fate of nicotine in the body influences the smoker's behaviour and contributes to dependence

It is important to consider the pharmacological properties of nicotine when we examine the mechanisms of tobacco dependence. Some of these properties (pharmacokinetic and pharmacodynamic) help us to better understand the strength of the dependence, even if the physiological and subjective effects of nicotine are rather limited and if other substances contained in tobacco smoke may also play a role.

Nicotine absorption is influenced by the type of tobacco and method of smoking. It occurs firstly in the mouth (particularly in cigar smokers) and then in the pulmonary alveolae. The amphiphilic properties of nicotine (which confer on it a degree of affinity for different media) facilitate its passage through the membranes, and is pH dependent. These properties have been used to develop nicotine replacement therapies (particularly patches and gum).
In an acid environment, nicotine exists in its ionised form and does not usually cross membranes, whereas in an alkaline environment it is rapidly absorbed, (particularly by the buccal and nasal mucosa, because of the thinness of their epithelium and their abundant blood supply). The use of tobacco products for chewing or taking as snuff therefore produces significantly higher blood nicotine concentrations as they avoid the first pass hepatic extraction and metabolism. Conversely, swallowed nicotine is absorbed in the small intestine enters the portal system and undergoes pre-systemic hepatic metabolism, explaning its low bio-availability (30-40%) after oral administration.

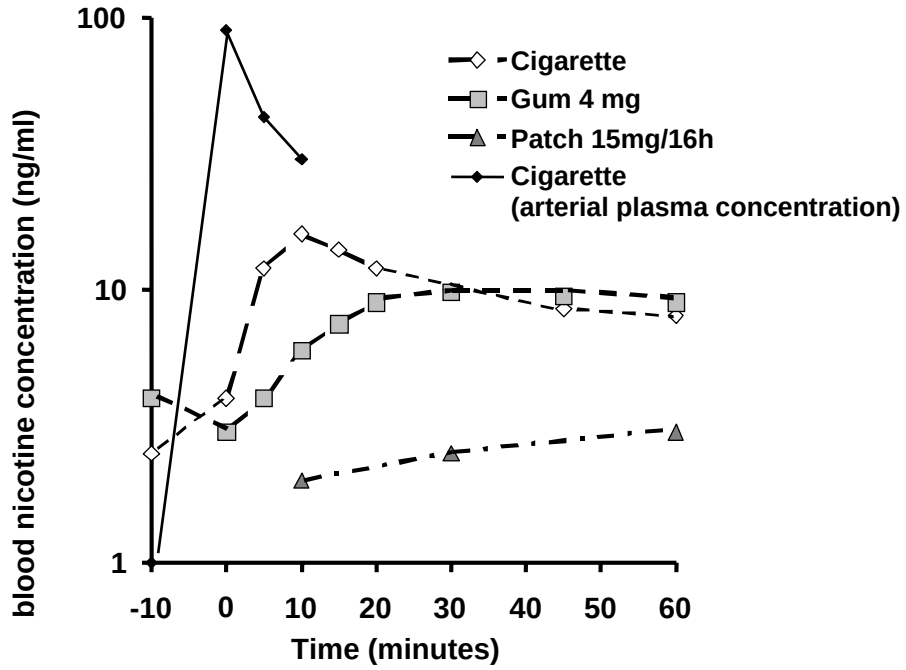
In contrast to pipe or cigar tobacco, blond tobacco (found in most cigarettes currently smoked) produces an acid smoke. The acid smoke is insufficiently absorbed even if held in the mouth for a long period of time. Inhalation is therefore needed to allow the nicotine to be absorbed by the enormous surface area of the alveolar epithelium. In the lungs, nicotine is rapidly absorbed by the systemic circulation: its absorption is facilitated as the blood flow through pulmonary capillaries is high, representing the entire circulating blood volume each minute. Plasma nicotine concentrations increase rapidly when a cigarette is smoked, reaching a plasma peak at the end of smoking the cigarette (approximately 10 minutes). In contrast, absorption from non-smoked products (chewing tobacco, snuff, nicotine gum) is subject to a certain delay and reaches a peak approximately 30 minutes after the beginning of administration. Nicotine absorbed from smoking tobacco therefore reaches the brain faster than after an intravenous injection and creates an imbalance between arterial and venous plasma concentrations. This does not apply to the case of absorption by the oral, nasal or transdermal routes (smokeless tobacco or nicotine replacement therapie) as in this case the absorption of nicotine occurs more slowly.

Nicotine is metabolised mostly in the liver. The renal excretion of untransformed nicotine is dependent on pH and urine flow and normally makes up 5 to 10% of total elimination. The elimination half life of of nicotine is approximately 2 hours, although this exhibits large inter-individual variability (1 to 4 hours).

The primary metabolites of nicotine are cotinine and nicotine N-oxide. Cotinine is the product of hepatic oxidation by cytochromes P450. This is then metabolized itself apart from less than 20%, which is excreted unchanged in the urine. The half life of cotinine is approximately 16 hours and it is therefore often used as a biomarker of nicotine consumption, particularly to confirm smoking abstinence in someone who has stopped smoking, or potentially to adjust nicotine replacement treatment.

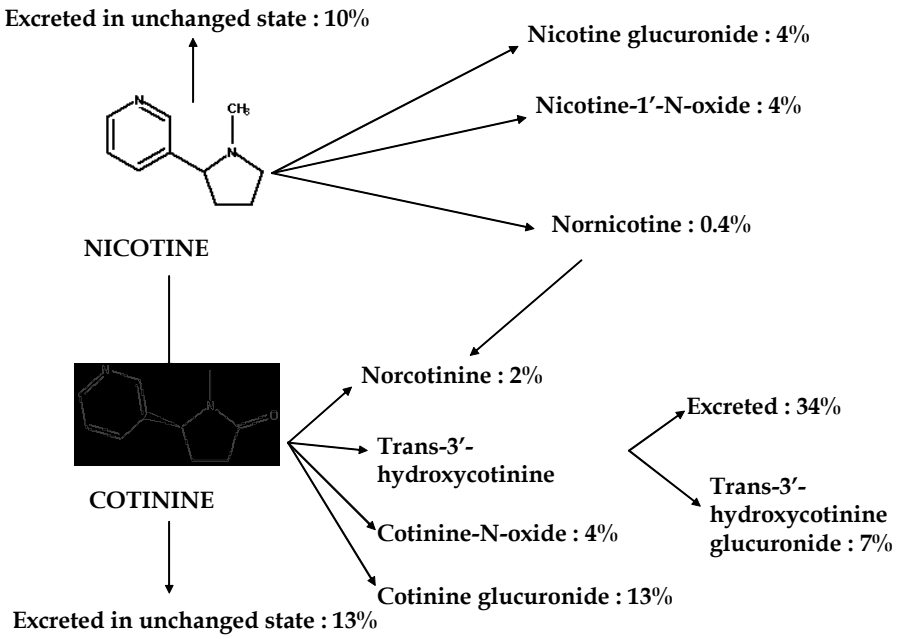
Very large inter-individual and sex-related variations in the rates of absorption and elimination of nicotine exist in smokers. Ethnic differences in the metabolism of nicotine have also been reported. Finally, any physiological event affecting hepatic blood flow such

as exercise, meals or consumption of medicinal drugs may influence the metabolism of nicotine.



Logarithm of arterial plasma concentrations after smoking of a cigarette and venous plasma concentrations after consumption of a cigarette, a 4 mg nicotine gum or a 15 mg/16h nicotine patch (from Henningfield, 1995).

The short half-life of nicotine is such that smokers must smoke frequently during the day and therefore obtain a large number of positive reinforcements (with each puff inhaled, i.e. 200 times per day in one-packet-a-day cigarette smoker). The negative effects (such as increase in heart rate) rapidly disappear during the everyday cycle of use, although as the acute tolerance of nicotine is incomplete a smoker can obtain positive central effects even at the end of the day. This tolerance disappears overnight: almost all of the nicotine is removed from the blood (because of its short half life) and the nicotine receptors regain their full potential for action (disappearance of acute tolerance and receptor resensitisation). The night-day cycle is therefore "ideal" to maintain everyday dependence. Chronic tolerance, which also makes a large number of the negative effects (for example nausea and dizziness) disappear, also undoubtedly contributes to this effect although has been less well studied. The pharmacokinetics (absorption, distribution, elimination) and pharmacodynamics (acute and chronic tolerance) of nicotine therefore make it an "ideal" psychoactive substance.



Metabolism of nicotine (from Vainio and Tuominen, 2001)

The percentages shown represent the relative amounts of the different metabolites present in urine.

Acetylcholine receptors are involved in the physiological effects of nicotine

Nicotinic acetylcholine receptors are present in many tissues in the body. They are ubiquitous within the nervous system and the expression of each isoform follows complex spatio-temporal patterns.

Nicotinic receptors form ion channels present in the plasma membranes of cells. They may exist in different interconvertible conformational states. Binding of nicotine stabilises the open and desensitised state(s). Opening of the channel allows positively charged ions, in particular, sodium and calcium to enter the cell. This activation of receptors by nicotine then modifies the state of neurones via two main mechanisms. On one hand, the movements of cations cause a depolarisation of the plasma membrane, which results in an excitation, particularly of neurones, but also by the activation of other voltage-gated ion channels. On the other hand, entry of calcium acts either directly or indirectly, on different intracellular cascades leading, for example, to the regulation of the activity of some genes or the release of neurotransmitters.

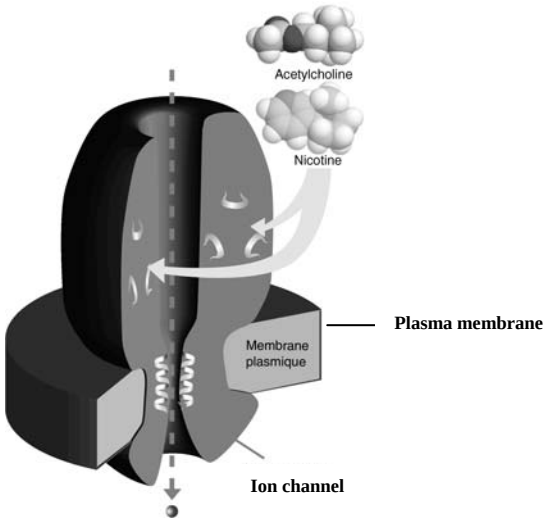
Nicotinic receptors are made up of five subunits, arranged symmetrically around the ion channel. Recent advances have allowed us to understand the structure of the extracellular and intracellular parts to almost atomic resolution. However, the structures known so far represent only one state of the receptors and do not yet allow us to understand the conformational changes and action of nicotine in detail. The subunits of the nicotinic receptors belong to a multigene family (16 members in human) and the assembly of combinations of subunits results in a large number of different receptors. These receptors, with highly variable kinetic, electrophysiological and pharmacological properties, respond differently to nicotine, at very different effective concentrations. This functional diversity allows them to take part in two major types of neurotransmission. Classical synaptic

transmission (wiring transmission) involves the release of high concentrations of neurotransmitter, acting on immediately neighbouring receptors. In contrast, paracrine transmission (volume transmission) involves neurotransmitters released by buttons or varicosities, which then diffuse through the extra-cellular medium until they reach their receptors, which may be distant.

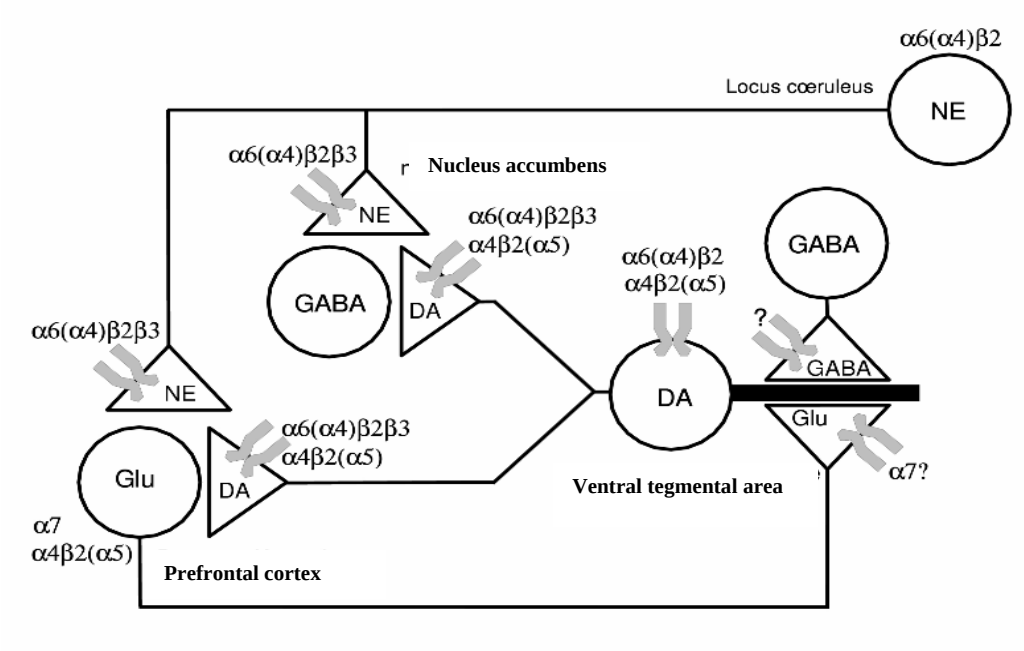
The receptor subunits are expressed by different cells in various territories. In particular, some subunits are expressed in all structures involved in dependencies such as, for example, the cerebral cortex, hippocampal formation (HF) and amygdala, septum, hypothalamus and basal ganglia. It must be noted however that major inter-species differences in distribution exist, even between close species such as the rat and mouse. Despite these differences, conserved expressions are observed, particularly between the dopaminergic systems of the rat and primates. Within the same cell, receptors are distributed in specific membrane subcompartments.

In the context of tobacco dependence, identification of the exact *in vivo* composition of the different receptors involved in the reinforcing aspects of nicotine has been helped by the availability of mutant mice carrying invalid subunits. The reinforcing effects of nicotine occur through modulation of cerebral dopamine release. The studies deal principally with identification of populations of nicotinic receptors responsible for this modulation. Dopaminergic neurones express large numbers of nicotinic receptors (α4β2, α6β2, α4α6β2 with variable participation from the α5 and β3 subunits), both on their axon terminals and on their somato-dendritic compartment. These receptors have been implicated in the regulation of nicotine-induced dopamine release. Some authors have hypothesised the involvement of α7 nicotinic receptors located on the glutamatergic terminals originating from the cortex which are in contact with dopaminergic neurones are involved. Finally, α6β2β3 and/or α4α6β2β3 nicotinic receptors located on nerve terminals originating from the locus ceruleus and controlling the release of noradrenaline in the prefrontal cortex may also be involved.

The major advances made over the last decade will accelerate further with the ability to identify nicotinic receptors with specific characteristics, and to identify their structure to a near-atomic level. This knowledge will help with the development of specific pharmacological effectors and allow pharmacological "cocktails" targeting several of these receptors simultaneously and differentially.



Diagrammatic representation of an acetylcholine nicotinic receptor



Location of nicotinic receptors identified in catecholaminergic structures of the brain

NE: noradrenaline; DA: dopamine; GABA: gamma-amino-butyric acid; GLU: glutamate

Environmental stimuli play a very important role in the activation of the reward system in smokers

Recent neurobiology findings have demonstrated that all substances which trigger dependence in humans (amphetamine, cocaine, morphine, heroin, cannabis, nicotine, alcohol, etc.) increase dopamine release in the nucleus accumbens. This nucleus forms part of a set of cerebral structures including the septum, amygdala, hippocampus and prefrontal cortex and called the "reward circuit". It defines the state of physical and psychological satisfaction a subject finds him/herself in at any one time. All of these cerebral structures receive dopaminergic innervation from the same structure of the brain, the ventral tegmental area (VTA). By modifying the levels of extracellular dopamine, psychoactive substances stimulate structures in the reward circuit and induce a sensation of satisfaction.

The activity of dopaminergic neurones increases with rewards such as eating, sexuality, etc. Learning leads to a situation in which it is no longer the reward which activates the dopaminergic neurones, but the signals heralding the arrival of the reward. During their development, each person constructs a set of signals specific to that person, perception of which allows the person to anticipate satisfaction and adapt to obtaining it. A signal not followed by a reward triggers frustration. By activating the dopaminergic systems intensely, taking a psychoactive substance leads the person to memorise events which are not physiological reality but because they are associated with taking the substance, make them dependent on it. Environmental stimuli are therefore particularly important in the smoker who has often over years developed many associations between specific situations and smoking. Presentation of the stimuli alone may lead to a compulsive desire to smoke.

The rewarding effect of smoking involves dopaminergic receptors

Some findings from humans suggest that stimulation of dopaminergic receptors may contribute to the reward effects obtained from tobacco use. Haloperidol, a dopaminergic

antagonist, produces an increase in tobacco use whereas dopaminergic agonists cause a reduction.

Dopamine acts through five receptors which are divided into two subfamilies, type D1 (sub-types D1 and D5) receptors which stimulate adenylyl cyclase activity via G proteins, and type D2 (sub-types D2, D3, D4) receptors, which are negatively bound to adenylyl cyclase.

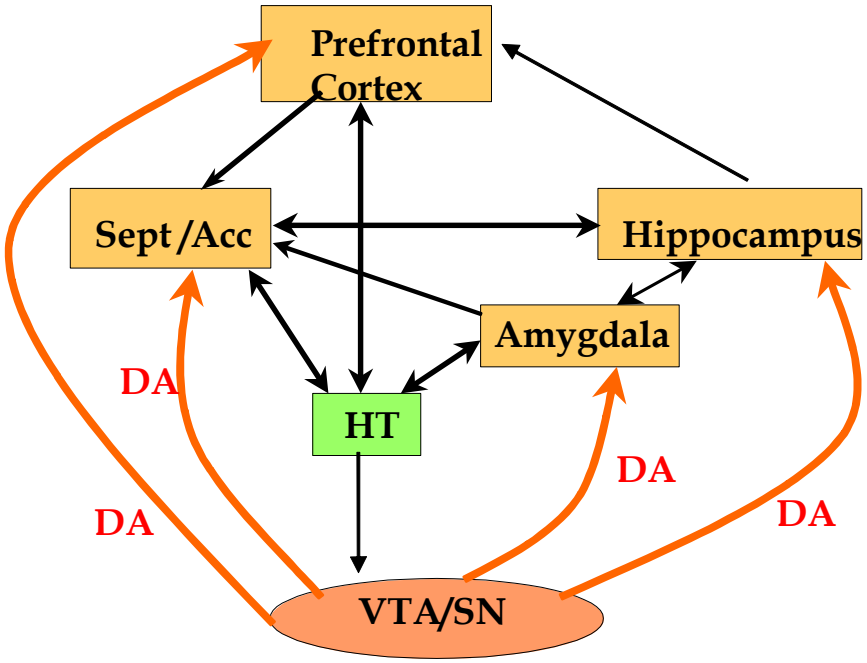
Mutant mice and selective pharmacological agents have been used to implicate D1, D2, and D3 dopamine receptors in drug dependence. These receptors are expressed in the nucleus accumbens, unlike the D4 and D5 receptors which are not or are almost not expressed in this nucleus. Only a few studies to date have selectively evaluated the role of D1, D2, D3 dopamine receptors in the reinforcing effects of nicotine.

Administration of 6-hydroxydopamine (a neurotoxin which destroys dopaminergic neurones) to the rat nucleus accumbens produces a reduction in nicotine self-administration. Most authors appear to take as accepted that dopaminergic pathways are involved in the reinforcing effects of nicotine.

In the rat, systemic administration of nicotine or direct injection into the VTA or the nucleus accumbens triggers dopamine release from the nucleus accumbens in the same way as other psychotropic substances. Changes in neurotransmission resulting from this have been implicated in the reward process and the dopamine released has been reported to contribute to the reinforcing effects of addictive agents. There is still little evidence from human beings or monkeys that this release of dopamine occurs in response to nicotine. It is the nicotinic acetylcholine receptors present in the VTA which appear to contribute to the rewarding effects of nicotine. However, nicotine receptors present on dopaminergic neurons desensitise in a few seconds or minutes, which would suggest think that prolonged release of dopamine involves other more complex in vivo mechanisms. Several models are based on the observation that there are very many subunits which form the nicotinic receptors and that depending on their composition and location, these receptors presents variable desensitisation kinetics. Nicotine may therefore activate or inhibit dopaminergic neurons in the VTA or through receptors located on dopaminergic, GABAergic or glutamatergic fibres.

During repeated drug administration, animals gradually develop an increased response for an identical dose: this is behavioural sensitization. Some authors have proposed that one mechanism explaining behavioural sensitization to nicotine is an increase in dopamine release. Induction of expression of D3 receptors has been described in the nucleus accumbens of rats conditioned to nicotine: selective ligands for this receptor type could therefore be of benefit in helping stopping smoking.

Smokers often cite stressful stimuli as the reason for relapses. The influence of environmental stimuli appears to be more important than the physical symptoms of withdrawal. With advances in cerebral imaging it is now possible to directly explore the cerebral structures involved in reactivity to conditioning stimuli in human beings, particularly using functional magnetic resonance imaging (fMRI). Presentation of these conditioning stimuli triggers activation of a neuronal network which, in particular, includes the VTA. This suggests that dopaminergic neurones are activated when conditioning stimuli associated with smoking are presented. The nucleus accumbens is a small structure which is difficult to examine with these techniques. Nevertheless, one study conducted in the rat did demonstrate that presentation of an environment associated with the effects of nicotine induced neuronal activity in the nucleus accumbens.



Cerebral reward circuit

This circuit may be thought of as being formed from several cortical and subcortical structures which are connected to each other by effector cells. All of these structures are innervated by modulating dopaminergic neurones, divergently from the VTA and the substantial nigra (SN). All of the information processed by neurones from the reward circuit converges on the hypothalamus, which itself interacts with mesencephalic dopaminergic neurones (VTA/SN). It should be noted that no information obtained from the external environment reaches the hypothalamus without having been pre-processed by at least one of the structures forming the reward circuit. DA = dopamine; Sep/Acc = septum/nucleus accumbens, double arrow = interaction between effector system and modulator system.

Dopamine appears only to be a link in a mesh involving other neuromodulators

Although the dopaminergic concept of dependence processes represents a considerable advance in our understanding of drug addiction, other neuromodulators such as noradrenaline, serotonin or acetylcholine also appear to be involved. In particular, noradrenergic neurones from the locus coeruleus are extremely sensitive to external sensory perceptions and the recent demonstration of a powerful link between noradrenergic and dopaminergic neurones should make us take all of the modulation systems into account. This appears to be particularly true for nicotine, the effect of which on dopaminergic neurones may only be marginal in its addictive activity.
A complex set of neuronal circuits is organised into networks in the brain in order to process sensory input, relay these to the cortex and finally translate them into behaviour or psychological outputs. The wide variety of behavioural responses requires some networks, and as a result some cerebral structures, to be selected depending on each situation experienced by the person. This selection is believed to be performed by another set of neurones, modulators, superimposed on the effector neuronal networks responsible for perceiving, processing and translating sensory effects into motor actions.

The neurotransmitters synthesised and released by effector neurones which make up the very great majority of central nervous system cells are GABA (gamma-amino butyric acid), glutamic acid, aspartic acid and possibly acetylcholine or a neuropeptides. The neurotransmitters for the modulator neurons are monoamines such as noradrenaline,

dopamine or serotonin. The cell bodies of these neurons are contained within the mesencephalon and send out projections towards the entire forebrain and hindbrain, to regulate the activity of the effector neurons. Although noradrenergic, serotonergic and dopaminergic modulator neurons are very much in the minority, only representing less than 1% of the 10 billion cells present in the brain, their transmissions are preferred targets for most psychotropic substances (antidepressants, neuroleptics, addictive drugs etc.). Dopamine very probably plays a role of final modulator of motor or psychological outputs in this circuit. Damage to the dopaminergic system may therefore result both in motor or mental disorders such as in Parkinson's disease or schizophrenia.

It has recently been reported that activation of dopaminergic neurons occurs as a result of stimulation of presynaptic nicotinic receptors, causing initial inhibition due to GABA release followed by excitation due to release of glutamic acid in the VTA. According to this dopaminergic theory of addiction, following an injection of nicotine, the nicotine increases the release of dopamine in the nucleus accumbens but, in contrast to what happens with other psychoactive substances, this effect is extinguished with repeated doses. In addition, whereas most addictive drugs increase locomotor activity in the rat and mouse, this effect is less pronounced with nicotine. As described earlier, tobacco smoke contains monoamine oxidase inhibitors (MAOI), which may be involved in maintaining extracellular dopamine concentrations.
Nicotine increases serotonin release in different structures of the forebrain. Although it has not been possible to identify nicotinic receptors on serotoninergic nerve endings, according to several authors serotonergic transmission plays a role in the dependence processes induced by nicotine. The detailed mechanisms of this relationship remain however poorly understood.

Similarly, nicotine intensely activates the noradrenergic neurones of the locus ceruleus, amongst other ways via stimulation of the peripheral nicotinic receptors and sensory fibres. It is not possible to exclude the possibility that this may be one of the predominant effects of nicotine in the central nervous system. Nicotine also modifies the activity of the hypothalamic-pituitary axis (HPA) and allows the release of prolactin and beta-endorphin.

Monoamine oxidase inhibitors present in tobacco smoke may be involved in the mechanism of dependence

Several authors have reported that tobacco users have reduced levels of activity of MAO the enzymes involved in degradation of neuromodulators such as dopamine, of up to 40%.

Substances such as harmane and norharmane or acetaldehyde in tobacco smoke have MAO inhibitory properties. It is possible that the MAO inhibitors contained in the tobacco smoke reduce the degradation of neuromodulators released by nicotine and therefore contribute to the mechanism of dependence. Behavioural sensitization to nicotine in the rat, which is only transient, becomes persistent when the animals receive an MAO inhibitor simultaneously with the nicotine. The authors therefore proposed that blockade of these enzymes acts synergistically with nicotine to activate the different neuromodulators and specifically the dopaminergic systems responsible for long term behavioural sensitization. This hypothesis could also explain why bupropion, an antidepressant which blocks noradrenaline and dopamine re-uptake has been found to be of help in stopping smoking.

Adaptation of the person to his/her environment involves permanent remodeling of the neuronal networks which may be affected by nicotine

The concept of plasticity classically groups together all of the changes affecting the morphology and wiring of pre-established neuronal networks. It has been shown that chronic administration of nicotine, like any other psychoactive substance, changes the morphology of neurons located in the regions involved in the reinforcing properties of drugs. It therefore significantly increases dendritic arborization (length and density) of neurons from the nucleus accumbens and frontal cortex. These changes are believed to alter the functional properties of the neurones and may contribute to the development of nicotine dependence.

It has also been discovered that certain regions of the adult brain, including in humans, are able to generate new neurones. This new form of plasticity called neo-neurogenesis or secondary neurogenesis is characteristic mainly of two areas recognised in all species: the subventricular area which borders the lateral ventricle and the dentate gyrus (DG) of the hippocampal formation (HF). The relationship between neo-neurogenesis and nicotine dependence has been examined by studying the impact of chronic nicotine administration (free choice or imposed) in animals. Such administration reduces the production of new neurones and increases the cell death processes in the DG of adult or adolescent rats. This fall in neurone production, also reported for other addictive substances (opiates, cannabis, alcohol), may be the origin of the cognitive defects seen in animals and involves the HF at least in part. They could also play a role in maintaining drug dependence behaviour by contributing to deregulation of the reward system in the rat.

Neurogenesis has also been studied in the context of research into the physiological bases of individual predisposition to develop drug dependence. It has been shown that neo-neurogenesis is reduced in subjects which are "spontaneously" vulnerable to dependence (the high reactive rat model) and in subjects which vulnerability has been induced by early deleterious life events such as prenatal stress. Although the mechanisms explaining this reduction are largely unknown, recent findings suggest the existence of a corticosterone-neurogenesis-drug addiction pathophysiological axis. By this, nicotine administered to vulnerable subjects would be increasingly effective when it acted in subjects who were characterised by low neurogenesis and a hyperactive hypothalamic pituitary adrenal axis, in whom the combination would increase dopaminergic transmission. When nicotine exposure occurs during the prenatal period in the rat, a sustained abnormal change was found in the organisation of certain cerebral networks, with a reduction in neurogenesis, cell changes (size and number of cells) and a reduction in dendritic tree arborization. It is conceivable that these structural changes may lead to the cognitive defects reported in adult rats that have been exposed to nicotine in utero.

Synaptic plasticity (persistent modification of the efficacy of synaptic transmission) is considered to be an information storage process. Chronic administration of nicotine changes the intensity of synaptic weights (measured by "long term potentiation and long term depression") in the HF and in the corpus striatum. These network changes due to neuronal activity are believed to play a major role in the construction of memories associated with drug dependence and to be relevant in explaining relapse phenomena.

Nicotine can also induce synaptic plasticity in the mesolimbic dopaminergic system. Activation of nicotinic receptors (containing the $\alpha 7$ sub-unit) in the VTA located on pre-synaptic glutamatergic afferent nerves initiates long term potentiation (LTP) by increasing

release of glutamate. This phenomenon, coupled to post-synaptic depolarisation, removes the inhibition of NMDA (N-methyl-d-aspartate) glutamatergic receptors causing LTP of glutamatergic afferent inputs on dopaminergic neurones. This LTP is believed to explain the prolonged release of dopamine despite rapid desensitisation of the nicotinic receptors located on the dopaminergic cell bodies

In summary, recent studies on animals indicate that chronic exposure to nicotine influences the structural and synaptic plasticity of the brain. The contribution of these changes to the pathophysiology of psychoactive substance used remains to be elucidated.

The weak reinforcing power of nicotine in the animal contrasts with the high dependence on tobacco in human beings

Substance dependence is described as being the result of reciprocal interactions between at least three essential factors: the individual, the substance itself and the context. Some of these interactions may be modelled and studied in animals.

Nicotine is a psychostimulant which produces measurable changes in behaviour following acute administration in the rat. Increase in exploratory activity (a psychomotor effect) is displayed over a relatively limited dose range, the highest doses being experienced as unpleasant. In addition, these locomotor effects are greater in adolescent than in adult rats. The tests used have also allowed anxiolytic activity to be identified during acute or sub-chronic administration of nicotine.
Repeated (approximately ten) injections of nicotine can change the long term behaviour of rats. This behavioural sensitization characterised by progressive increase in psychostimulatory and anxiolytic effects. This sensitization can be linked to changes in activity of the dopaminergic pathways involving glutamatergic and serotonergic mechanisms. The intensity of sensitization depends on intrinsic factors (strain, sex) and environmental factors such as stress. It is expressed preferentially in a context in which the animal is habituated to receiving nicotine.

In addition, if an animal is sensitized to the effects of nicotine, it is also sensitized to other psychotropic substances and vice versa (cross-sensitization). Chronic alcohol exposure in the mouse facilitates the behavioural sensitization induced by repeated administration of nicotine, although this effect is only seen if the animal is placed in the environment in which it has consumed alcohol, highlighting the importance of environmentally conditioned effects. Secondly, nicotine administered to the mouse potentiates many of the effects of cannabis (delta 9-tetrahydrocannabinol), such as analgesia, hypothermia and its anxiolytic and reinforcing effects.

The subjective effects of a drug play a key role in addiction. The sensations perceived by the animal following administration may be neutral, pleasant or adverse. They may be associated with a place (preference for or aversion of the conditioned place) or with a behavioural response (self-stimulation, self-administration).

The conditioning procedure or place preference can be used to measure the intensity of the hedonistic value, the memory which the substance leaves with the animal. The aim of this conditioning phase is to associate the interoreceptive effects of the drug with a particular context. If during the test (without injection) the animal prefers the compartment associated with injection of the drug this is described as rewarding. This protocol allows an animal to be tested long after the conditioning phase. With nicotine, the results appear to depend on the age of the subject. In a young rat (adolescent) therefore, a considerable preference is seen for

the environment which was associated with nicotine administration, whereas place preference is less pronounced in the older rat.

The experimental model of intravenous self-administration of a psychoactive substance demonstrates the active behaviour of the animal to obtain the substance and is therefore related to compulsive drug taking in the drug addict. Self-administration of nicotine has been demonstrated in many species (rat, mouse, monkey etc.). Certain external factors facilitate taking nicotine (rapid injection, taking at night, restricted diet, presence of environmental stimuli etc.). In addition, large individual differences exist. Animals which display high exploratory behaviour therefore consume more nicotine. This increased vulnerability may be induced experimentally by in utero stress or stress applied to the adult animal.

Self-administration of nicotine by animals is not, however, a very intense behaviour and is relatively fragile compared to the effects of other addictive substances. When the rat has the choice it prefers cocaine to nicotine, and the animal tends to give up if the effort required to obtain the nicotine becomes too great.

It therefore emerges from all of the available studies in animals that the reinforcing effects of nicotine are weak compared to other addictive substances. This finding contrasts with the very high dependence of smoking in human beings and may be explained by several factors.

In human beings the methods of consuming tobacco are different from those of other psychoactive substances and the current animal models do not take this distinctive factor into account (in particular inhalation of smoke).

It is likely that other substances which are perhaps themselves addictive or which potentiate the effects of nicotine are contained within tobacco smoke (MAOI, etc). Only few studies have examined this field.

The contexts associated with use of tobacco facilitate and maintain compulsive tobacco consumption.

Many affective, relationship and psychological factors drive an individual to consume tobacco although these factors are difficult to model in animals.

The utility of an animal model depends on its ability to take account of the essential characteristics of human behaviour which are modelled in order to allow systematic investigation of these features. Whilst intravenous self-administration of nicotine is a good model to demonstrate the addictive nature of nicotine, much remains to be done to find a method of nicotine consumption in animals which mimics the frequency of tobacco use in human beings.

Local sensory stimuli associated with the cigarette may maintain tobacco dependence

The behavioural effects associated with smoking and the peripheral sensory effects of tobacco on the upper respiratory and bucco-pharyngeal regions may contribute to the initiation, development and maintenance of dependence.

Smoking behaviour is associated with sensory effects such as sensations of heat, taste and smell, and specific sensations in the upper respiratory tract (which may be irritant in nature) or further still, the pleasure provided by inhalation of smoke. In the absence of studies on the peripheral sensory effects of tobacco per se (cigare, pipe or chewed tobacco) the data relate to the impact of the sensory effects of the cigarettes.

The local sensory effects of the cigarette, whether due to the smoke, tobacco, its constituents or menthol in mentholated cigarettes represent a set of stimuli which may form part of the conditioned reinforcement of the smoker. When associated with repetitive, compulsive behaviour they may contribute to the establishment of the positive reinforcing circuits and help to maintain tobacco dependence.

These sensory effects of the cigarette are to a large extent due dose-dependently to the nicotine present in tobacco smoke. However, when administered intravenously, nicotine causes few if any sensory effects, suggesting that the specific effects of nicotine are associated with stimulation of the nicotinic receptors present in the mucosal membranes of the upper respiratory tract. Studies have shown however that smoking denicotinised cigarettes appear to bring satisfaction to the smoker and relieves the smoker's desire to smoke. Furthermore, the possibility that other substances at present unknown or unstudied, present in tobacco smoke may also have sensory effects has not been excluded. A few studies addressed the question whether addition of menthol to cigarettes play a role in their sensory effects rendering them more addictive. The studies in question however do not allow us to confirm with certainty that the sensory effects of cigarette mentholation contribute to initiation or persistence of tobacco dependence.

Future research studies should help to identify which substances are liable to produce peripheral sensory effects (nicotine, other substances in tobacco, or in tobacco smoke etc.) and to understand their role in craving/urge for tobacco and the development and maintenance of tobacco dependence, together with their possible contribution to the efficacy of replacement therapies administered via the buccal route (gums, oral or sublingual tablets).

Nicotine improves cognitive functions and/or reduces deterioration of these functions during withdrawal

Smokers have different reasons for smoking, although most claim that it produces both intellectual stimulation, principally with the first cigarettes of the day, and a relaxing effect, particularly in stressful situations. Most studies conducted over the last thirty years have focused on the effects of nicotine, the principal alkaloid of tobacco. It is undoubtedly an over-simplification to attribute the effects of tobacco only nicotine, although there are almost no studies on the other components of tobacco smoke. The effects of nicotine on cognitive processes however are interesting as they are probably reinforcers of smoking behaviour. Tobacco dependence may be maintained by an association of positive effects on cognitive functions and avoidance of the negative effects of withdrawal.

The question to be answered is whether the improvement in cognitive performances seen after cigarette smoking is due principally to relief of the deterioration in performance associated with abstinence, direct facilitation of these performances or a mixture of both effects. Nicotine withdrawal causes uncomfortable changes in mood and behaviour which may discourage smokers from attempting to stop or cause a relapse in an abstinent smoker. Many studies have demonstrated that nicotine improves performances in a large range of tasks testing selective or sustained attention, distraction, learning and memory, together with motor control. The utility of the results of these trials is however limited by methodological problems.

A review of trials conducted since 1994 (randomised, controlled trials with measurement of plasma nicotine concentrations, variety of tests etc.) have demonstrated that nicotine

administered to abstinent smokers has positive effects on their cognitive functions. According to these studies, nicotine influences attention mechanisms (particularly visual), subjective effects (such as reductions in withdrawal symptoms) and mood. The action of nicotine on cognitive functions can only be identified using complex tasks or in people with deficits (patients suffering from Alzheimer's disease, Parkinson's disease, schizophrenia, attention deficit hyperactivity disorder, Gilles de la Tourette syndrome or Down'syndrome).

Pharmacodynamic factors should also be taken into account in studying the effects of nicotine on performance in human beings, as we do not yet know whether these are subject to acute or chronic tolerance. Facilitation of performance perceived as reinforcement may flatten during the day, like the other effects of nicotine (for example cardiovascular). Studies of chronic tolerance and behavioural effects of nicotine are also needed. To do this it may be useful to compare regular with occasional smokers.

Prenatal exposure to tobacco may influence the risk of future dependence

The question of the role of pre or peri-natal exposure to tobacco in the risk of subsequent development of tobacco dependence rises for the following reasons:

- (limited) experimental data suggest that prenatal exposure to nicotine may lead to subsequent vulnerability to nicotine dependence ;
- nicotine and other components of tobacco smoke cross the placental barrier and smoking has demonstrable effects on different aspects of foetal development and very likely effects on development of the brain. Thus, prenatal exposure could also be involved in the risk of dependence ;
- currently in France, 25% of pregnant women smoke. With such a high frequency, if prenatal exposure to tobacco leads to an actual risk of subsequent dependence the public health impact may be considerable even if the level of risk is relatively low.

Whilst the question is relevant, it is methodologically difficult to conduct epidemiological studies designed to answer it. The question requires cohort studies followed up over a long period of time which clearly distinguish "simple" tobacco use from dependence, and which allow the effects of in utero exposure to be separated from those of many other factors which come into play throughout life. At present the knowledge available is relatively limited and is based on a very small number of studies, coming mostly from one American team. This team's results point towards an increase in risk of tobacco use in the children of mothers who smoked during pregnancy which the team considers to be greater in girls than in boys. A recent study from another American team examined tobacco dependence in young adults (17 – 39 years old) and found an increase in the risk of dependence only in those whose mothers smoked at least 20 cigarettes per day during the pregnancy, independently of sex.

These studies, which are difficult to conduct, need to be replicated in other populations in order to confirm or exclude the relationship described above, to quantify the role of prenatal exposure in the development of dependence compared to many other personal, environmental, family or social factors which come into play and to determine how vulnerability to dependence related to prenatal exposure, if this exists, interacts with these other factors.

Genetic vulnerability factors interact with many environmental and behavioural factors

As for all of the other psychoactive substances, people are not equal in terms of vulnerability to the dangers of smoking. Some people are more sensitive to the aversive effects of nicotine when first exposed to tobacco whereas others are more vulnerable to the reinforcing effects and more or less quickly become tolerant. Some people limit themselves to occasional smoking while others rapidly become regular smokers. Furthermore, some people who are dependent on tobacco may stop and remain abstinent whereas for others this is difficult to achieve.

Two recent meta-analyses incorporating 43 studies (based on twins, families or adoptions) have examined the respective roles of genetic and environmental factors in the different stages of smoking: initiation, persistence, stopping and abstinence. For each of these stages, the factors involved depend on age of the cohort and on gender. According to all of these studies, being a regular male smoker depends 61% on genetic factors and 39% on environmental factors. The findings are very similar for women, with 63% for genetic factors and 37% for environmental factors. In male adolescents, smoking initiation depends more on environmental factors which contribute up to 70% to smoking initiation. These findings provide us therefore with information which must be taken into account in terms of prevention of smoking initiation in the adolescent (environmental factors) and in helping cessation in the adult (genetic factors).

Epidemiological studies, however, provide no information about the nature of the genetic factors involved. It is clear that the different components of smoking and co-morbidities related to gene assortment may be common but also different. The number of genes involved in each assortment and their relative weight is not known, although it is reasonable to assume that polymorphisms (variants) of several tens of genes contribute to the variance.

Knowledge is beginning to emerge however in this very complex field of the genetics of smoking. Association studies performed on medical series containing various categories of smokers, ex-smokers and non-smokers and examining polymorphisms of different candidate genes have been able to identify the involvement of certain genes. Three major classes of genetic vulnerability factors are recognised. These bring together common or different factors for different stages of consumption depending on personality traits or age, and are related to other addictions or certain psychiatric disorders (co-morbidities). These contribute to smoking with different weighs.

The first class of genes involves the metabolism and bio-availability of the addictive substances in tobacco (nicotine etc.) and their metabolites (cotinine etc). From a pharmacokinetic and pharmacogenetic point of view it is established that the cytochrome P450 CYP2A6 is the major route (80%) of oxidation of nicotine, cotinine and other metabolites. “Slow metabolisers” smoke less, are less likely to have lung cancers and stop smoking more easily. However, despite the aboundant literature on the subject and because of different inter-ethnic differences in the frequency of deleterious or duplicated alleles (Asians versus Caucasians), the protective role of the absence of CYP2A6 remains controversial. Nevertheless, it has been found that oral use of CYP2A6 inhibitors reduces tobacco consumption and helps patients stop the same way as was found in subjects with defective alleles. The CYP2A6 gene however is not the only gene explaining inter-ethnic and inter-individual differences in smoking behaviour. Other genes (CYP2E1, UDP-glucuronosyl-transferase I –UGT) involved in the metabolism of nicotine also offer interesting research avenues. Other potentially addictive substances in tobacco may present research alternatives although the metabolic pathways involved are not yet known.

Variants of genes such as CYP2A6 may predict the response to nicotine replacement therapies, and other variables such as CYP2B6 (which metabolises nicotine and bupropion in the brain) may predict response to antidepressants. Reduced activity of the enzyme CYP2B6

coded for by an allele present in 30% of Caucasians is associated with more severe withdrawal symptoms, mostly in women. According to a recent study, women carrying this allele respond well to treatment by bupropion, with a 54% abstinence rate versus 19% with a placebo. Identification of polymorphisms of different genes should enable treatments to be tailored to the genetic background of the patient and to provide more effective treatment.

The second class of genes is those involved in the mechanisms of action of the addictive substances in tobacco. Association studies to date have identified the involvement of 21 genes in different aspects of tobacco addiction. These genes belong to the family of nicotinic receptors or are associated with the dopaminergic, serotoninergic or noradrenergic pathways or alkaloid for opioid, cannabinoid or other neuromediator receptors which modulate the reward system.
The third class combines wide networks of genes which may be directly or indirectly involved, such as the gene for variability of responses to stress, tastes, smells or susceptibility towards obesity.

The studies performed to date indicate that genetic inheritance of the number of cigarettes smoked (which is high: 85%) is associated with variants of 7 different genes. The variants of 7 other genes have been associated with starting and those of 2 genes with age of starting. Most of these studies only examined a very small number of genes (1–3) and the component of variance explained by the studies remains low (0.4 to 2%). A very small proportion of the possible candidate genes (or pathways) has been examined and only three examples of gene-gene interactions have been described. One study (conducted in context of pathological gambling) tested 31 genes for the dopaminergic, serotoninergic, noradrenergic and GABAergic pathways (and others) and demonstrated that the dopaminergic pathway is predominantly involved (9% of variance) and that the other pathways together explain 26% of variance from the 7 gene variants. In view of the modest effects attributable to each of the genes studied to date it is inconceivable that a single gene has a predictive role or could be used for predictive purposes. Each person carries at least one susceptibility allele and at least one protective allele, which could anihilate their respective effects.

In order to identify all of the genetic factors involved, interactions between the different variants and environmental factors, are essential to study, based on several tens or even hundreds of genes. Research is currently being directed towards the investigation of haplotypes which are well characterised and representative of an ethnic group, incorporating interactions between genes belonging to several pathways (metabolic, neurotransmission or signalling) and interactions with the environment, and protective or harmful behaviour, and with respect to age and gender.

Interactions between several genes (three cases reported to date) may have a significant influence by greatly increasing the overall risk compared to the risk associated with each gene taken individually. The reasoning methods for these multi-gene models therefore have nothing to do with those which have been used to date for rare single gene disorders. One might imagine that in the future, identification of a large number of vulnerability factors will allow prevention to be better organised for people at increased risk, with respect to smoking (adolescents at higher risk of dependence etc.), to plan cessation and sustained abstinence better and to offer the most effective strategies. By no means, however, do these studies confirm the concept of the "safe cigarette" for some people.
Communication policies could therefore take more into account of the dangers of tobacco in certain sub-types of smokers while delivering their messages (genetic background, stage, age, gender, ethnic group, personality traits, cognitive disorders etc.) and offer tailored prevention strategies.

Psychological and psychosociological variables contribute to initiation and persitence of smoking

Not all people exposed to smoking will develop dependence and it is likely that some people are more susceptible than others. Psychological and psychosociological variables contribute to smoking initiation, to maintaining the habit and to the development of motivation for stopping smoking.

The social factors involved in starting smoking and then maintaining dependence on tobacco partly explain the changes in prevalence. The fall in the number of smokers seen in France between 1953 and 2000 due to the considerable fall in male smoking should be considered in parallel with the increase in tobacco sales. These findings suggest that the greater the drop in prevalence the more smokers are different from one period to another (fewer in number, nowadays but consuming more). There therefore appears to be a sub-group of smokers who are sensitive to social constraints, a sensitivity which enables them to stop smoking. With the prevalence of smoking estimated to be approximately 30% today, one might hypothesize that as applied to the United States, Sweden and United Kingdom, the proportion of smokers who are entirely insensitive to the social environment is closer to 10% than 30%. Social determinants alone may explain the behaviour of some smokers (at present considered to be dependent) and explain the non-biological component of dependent behaviour in all dependent smokers.

A number of personality theories exist which formalise the individual differences in tendency to seek or avoid tobacco. The dimensions implicated in smoking which emerge from the literature have been obtained from three behavioural models of personality: sensations seeking, novelty seeking and extraversion. Recent work on sensations seeking strengthens the hypothesis that this dimension may promote entry into the dependence, and is involved more in smoking initiation. The avoidance of distress dimension appears to be more closely linked to dependence and describes the anxiolytic effect sought by smokers through smoking. Interpretations of the effects and role which tobacco plays in emotion management in a person should therefore be approached in future research through hypotheses of defective physiological activation or defective neurobiolgical activity.

There are similarities, but also differences between smoking adolescents and adults

Although the major smoking-related diseases develop in adults, their origin often lies in the development of smoking dependence during the juvenile, particularly adolescent period.

It is estimated that several thousands of children and adolescents experiment with cigarettes each day in France, and of these, 30 to 50% become daily smokers. A insignificant proportion of these people will progress into dependence, which will subsequently make it difficult for them to begin the smoking cessation process.

There are both similarities and differences between smoking in young people and in adults. Young people, principally in the experimental stage, rarely smoke regularly or every day. In particular, they smoke for the immediate pharmacological benefits experienced, sometimes to control their weight and to respond to environmental stimuli. Conversely, the symptoms which develop during withdrawal are similar in young and adult smokers and interfere with the intention to stop. Secondly, cognitive performance deteriorates in the same way during periods of abstinence in adolescents and in adults.

Smoking is often the first dependence in adolescents. It is significantly associated with increased risk of alcohol dependence and dependence on other psychoactive substances in early adulthood.

The early age at which smoking is initiated (first puffs, first cigarette) is a major public health concern. Several studies have shown that the earlier initiation occurs the greater are the risks of becoming dependent on tobacco, of smoking in adulthood and of experiencing difficulties in stopping. Smoking in the mother or siblings, behavioural problems, peer pressure and ease of obtaining cigarettes from parents or other adults are also factors which promote starting smoking.

Starting smoking before the age of 14 years old (currently the average age of initiation in France) is statistically significantly associated with negative events in childhood such as mistreatment, family violence, mental disorders within the family or use of illegal substances.

Progression from smoking initiation to dependence is a rapid process in adolescents, which ranges from a few months to a few years depending on the studies and the evaluation tools used to define the threshold for dependence. In adolescents in particular, the tools used intentionally do not include the number of cigarettes smoked, which is usually less than in adults, very variable and not directly related to the presence of dependence. These tools are designed to offer a sensitive and specific screening method for tobacco dependence in adolescents, the questions are based on the symptoms of dependence and withdrawal.

A large number of adolescents who smoke express a desire to stop, although three-quarters of those who try to stop fail. Young people are not sensitive to the same messages as adults. According to some studies, the minimum advice which any health care worker can give is effective in young people. It is therefore of major public health importance to construct and design specifically targeted interventions towards adolescent smokers.

Therapeutic smoking cessation trials need to be performed in order to evaluate medical drug treatments in young smokers. These trials will probably test lower doses of nicotine compared to those recommended in adults and make more frequent use of individual dose adjustment to reduce the adverse effects and increase the effectiveness of and compliance with treatment. Predictive indicators for failure also need to be identified. Early interventions (which will have to be evaluated) designed to treat smoking in adolescents will undoubtedly help to prevent the initiation and maintenance of dependence.

Improved evaluation of maturity to change in the trajectory of a smoker, to optimize assistance during cessation

Several studies have shown that the risk of developing dependence after one or more exposures is particularly high in the case of tobacco. The time required for dependence to develop varies greatly from one person to another but also across studies. Dependence has been found to be established within one year after starting daily smoking in 95% of smokers (in an American population between 15 and 54 years old).

As described above, dependence on tobacco is characterized by tolerance of the adverse effects of nicotine, expectation of both pleasure and psychological relief, and by a withdrawal syndrome when smoking is stopped. In addition, the population of dependent smokers has more psychiatric co-morbidities, all diagnoses combined. The prevalence of alcohol dependence ranges from 15% (current alcoholism) to 35% (past history of alcoholism) in

heavy smokers. Not only are smoking problems more frequent in alcoholics but their consumption of cigarettes and level of dependence are greater.
Alcoholic smokers are more dependent on alcohol than alcoholic non-smokers. The co-morbidity relationship between depression and tobacco dependence does not appear to be causal but rather, linked to sharing common, mostly genetic, risk factors. The risk of suicide is increased in smokers and appears to be higher in female than in male smokers. Heavy smoking during adolescence appears to be a risk factor for developing anxiety disorders such as agoraphobia, generalized anxiety disorder or panic disorder. Conversely, social phobia appears to be a risk factor for developing tobacco dependence. The prevalence of smoking is particularly high in schizophrenics (two to three times higher than in the general population).

Different instruments have been developed and then refined to predict the diagnosis of tobacco dependence. The Fagerström test for nicotine dependence (FTND) is widely used quantitatively to measure nicotine dependence.

According to the "Baromètre santé 2000", approximately 60% of 15–75 year old smokers say that they wish to stop smoking, and of these more than 80% say that they have already stopped for at least one week. The majority consider stopping on their own initiative as the means of stopping smoking (50% stopping suddenly and almost 30% stopping gradually). Almost one quarter of people who wish to stop consider using nicotine replacement treatment (NRT).

The treatments currently available to help stopping smoking are nicotine replacement therapies, bupropion treatment and patient support with cognitive-behavioural therapies. According to all of the studies examined by Afssaps, nicotine replacement help to double the smoking abstinence rate. 18% of smokers who have received NRT are abstinent at one year compared to 10% in a placebo group. Bupropion is similar in efficacy to the NRT. There is at present no proof that the association of bupropion with NRT is more effective than either treatment used alone. Cognitive-behavioural therapy helps to double the smoking abstinence rate at 6 months.

Different studies have managed to identify the factors associated with a high success rate for smoking cessation. Apart from strong motivation, the predictive indicators for success are a high socio-economic or educational level, low consumption of cigarettes, late age in starting smoking, short history of smoking and a long period of time between waking up and smoking the first cigarette of the day. It also seems necessary to take personality factors (sensations seeking, novelty seeking, extroversion, etc) and associations with psychopathological vulnerabilities into account to tailor the management and messages to the different populations.
Descriptive instruments to characterize change dynamics in smoking cessation have been developed progressively in order to take into account of the psychological level of advancement of a person who wishes to stop smoking; these tools help to better tailor the assistance to the person in order to optimize the chances of success. According to the trans-theoretical model, the smoking cycle contains five states: the happy smoker (who is not ready to attempt to stop, pre-contemplation stage), the ambivalent smoker (uncertain, contemplation stage), the decided smoker (ready to stop, preparation stage), the smoker who has stopped (action) and the confirmed abstinent smoker (maintenance).

Historically, four models of change have been described: (1) the persuasion model: changing values to change acts, (2) the engagement model: obtaining acts and changing values by countering, (3) the awareness model: a contradiction in the person's value is identified and (4) the counter-conditioning model: contradiction is introduced into the acts. Whilst taken individually these four models are not the highest performing, each one is suitable at a

particular time in what can be called the "trajectory of change" of the smoker. In addition, knowledge of spontaneous change in non-assisted smokers allows us to envisage differential interventions which are better founded, less intuitive and probably more effective. Two simple rules therefore apply in the context of considering prevention and clinical intervention :

- when the patient is not motivated, classical informative intervention processes must be used; the method does not need to be negative or imply culpability. These smokers at the start of the change process need informing, predicting and alerting our suitable preventative strategies ;
- when the patient is informed and conscious of the dangers it is more appropriate to consider concrete encouragement towards the act (firstly setting easy to reach objectives to increase feelings of personal effectiveness, making the person think about behavioural replacement strategies and methods of self-reward, etc).

This is currently leading researchers to propose increasingly sophisticated models allowing the maturity of individual smokers (vis-à-vis their motivation to stop smoking) to be measured and therefore to target the interventions better.

Recommendations

Whilst use of tobacco is clearly influenced by the social and affective environment of the individual, tobacco dependence appears to be more strongly influenced by personality, genetic factors and psychopathological vulnerability. In addition, individual reactivity to the different constituents of tobacco and the sensory effects associated with inhalation of cigarette smoke may also contribute to the development and maintenance of dependence. In this context, all of the environmental stimuli associated with the use of tobacco are liable to lead to conditioning of the smoker. As for other psychoactive substances, one of the important characteristics of tobacco dependence is the apparent inability to stop consumption, despite knowledge of the adverse effects of tobacco on health. A combination of these different stimuli may produce compulsive desire to use tobacco, maintain dependence and is a cause for relapse even after long term abstinence.

One of the major obstacles to stopping smoking is the fact that smokers seek stimulation of their intellectual functions, increase in their concentration ability, relaxation or even relief from a stressful situation through smoking of cigarettes, in addition to their hedonistic effects. In addition, for many smokers abstinence is accompanied not only by the unpleasant sensations associated with the withdrawal syndrome but with the perception of deterioration in their intellectual capacity. It has not as yet been clearly established whether the intake of nicotine causes real facilitation of cognitive performance, whether it reduces the unpleasant consequences of withdrawal on these performances or whether these two processes co-exist.

Although the role of information about the adverse effects of tobacco on health does not appear to significantly influence the long term abstinence rate in the smoking population, recent studies have been able to identify different predictive factors for successfully stopping smoking. Taking these individual or environmental factors into account, combined firstly, with the development of relevant models to improve knowledge about behavioural-change dynamics in the trajectory of candidates for stopping smoking and secondly with psychological and pharmacological support processes, may help to improve smoking cessation figures.

In view of the large number of tobacco users in France at present – despite political, social and economic interventions – the damaging effects of tobacco use in terms of public health and the resultant costs, further research into smoking appears to be essential. In addition, the neurobiological mechanisms which underpin the tobacco dependence processes are still largely unknown. Future research will also benefit greatly from the development of a multi-disciplinary structure. At present, most work is focused on nicotine: the current state of research suggests that other substances present in tobacco smoke or their metabolites may help to explain the high dependence liability of smoking. It appears necessary for research groups into the chemistry and pharmacology of tobacco to provide tools (experimental cigarettes, specific nicotinic ligands etc.) to explore these new paths, and to improve understanding of smoking behaviour and dependence.

Preventing smoking in adolescents and managing smokers

TO DEVELOP AND EVALUATE PREVENTION PROGRAMMES THAT TARGET THE FACTORS INVOLVED IN SMOKING INITIATION IN ADOLESCENTS

Smoking initiation among adolescents is influenced by the presence of smokers in the environment, peer pressure and ease of obtaining cigarettes from friends, parents and other adults. In addition, during the experimentation phase, young people who will become dependent upon tobacco obtain immediate and greater pharmacological benefit than other young people. For these reasons, health professionals must be informed about the risk factors in order to provide early management to adolescents who are still in the experimental phase of smoking. Starting smoking early in some adolescents is promoted by adverse events occurring during childhood, the presence of mental disorders and consumption of alcohol or psychoactive substances.

Dependence on tobacco develops rapidly (from a few months to a few years) after initiation. It is therefore essential to implicate health professionals, families and teachers to offer adolescent smokers interventions (pharmacological or otherwise) designed to stop smoking as early as possible after the first cigarettes smoked. The age of starting smoking is a predictive factor for future dependence and the earlier the person starts the higher is the risk becoming dependent. The expert group recommends that prevention programs be developed in parallel, at all levels (medical, social, economic, educational), to delay starting smoking, and that these be evaluated.

SET UP SERVICES AND STRATEGIES TO ASSIST CESSATION WHICH ARE SUITABLE FOR AGE AND IN SPECIFIC POPULATIONS

In adults

Successful smoking cessation requires strong motivation, and during his/her trajectory, the candidate for smoking cessation will pass through different phases, the characteristics of which influence the likelihood of success. In light of recent knowledge it is important to consider the mechanisms of behavioural change dynamics in intervention methods to assist cessation.

The withdrawal syndrome is a particularly unpleasant syndrome for the smoker who is trying to give up and is a factor which promotes relapse. The expert group recommends that treatment (pharmacological and non-pharmacological) be tailored to the profile of the smoker and that all scientific knowledge be used to research treatments which can reduce the symptoms associated with withdrawal and the risk of relapse, which remain very high with current treatment methods.

In adolescents

Dependence is acquired with less tobacco use in adolescents than in adults, implying the need to develop more sensitive instruments to measure this. It appears that a large number of adolescents who smoke regret that they started to smoke and express a desire to stop. It is of great importance that they be supported in this process by their family, the educational environment and health professionals. The expert group recommends that all actions be

taken to sensitize the adult population which is liable to help adolescent smokers undertake the process to stop. It also recommends that consultations and exchange groups which are suitable for adolescents, easy to access and compatible with their lifestyle be developed, and that the efficacy of management of this population, including the use of nicotine replacement therapies, be evaluated.

In pregnant women

It is known that like other components of tobacco smoke, nicotine easily crosses the placental barrier and that smoking during pregnancy has consequences on the development of the foetus, particularly on the foetal brain. In public health terms, the high number of women who smoke during their pregnancy raises the question of the impact of in utero exposure in the development of subsequent tobacco dependence. As such, a small number of experimental animal studies suggest that prenatal exposure to nicotine during a critical period of development may be a vulnerability factor for dependence. Epidemiological studies (which are still insufficient) point in the same direction. In view of this work the expert group recommends that smoking cessation be encouraged in pregnant women and even, if possible, in women who are planning a pregnancy. In addition it would seem prudent to choose first line for non-pharmacological assistance for smoking cessation.

The expert group recommends that the benefit/risk ratio of nicotine substitutes be evaluated in the specific population of pregnant women.

Develop research

TO CONTINUE THE IDENTIFICATION OF NICOTINIC RECEPTOR SUBUNITS AND/OR THEIR COMBINATIONS WHICH ARE LIABLE TO BE INVOLVED IN THE DEPENDENCE PROCESS

A very large number of nicotinic receptors have been identified with different kinetic, electrophysiological and pharmacological properties, and as such are liable to respond differently to nicotine. Their subunit composition is a determining factor in their contribution to dependence. Identification of new receptors and research into their atomic structure may lead to the identification of new therapeutic targets. In addition, the discovery of increasingly specific pharmacological effectors makes it possible to envisage the development of pharmacological "cocktails" which act differently on several nicotinic receptors.

The expert group recommends to continue research into nicotinic receptor analysis and their involvement in dependence. It also recommends to increase the search for more specific and more effective nicotine replacement therapies.

TO UNDERSTAND THE RELATIONSHIPS BETWEEN EFFECTOR AND MODULATOR SYSTEMS IN THE DEPENDENCE MECHANISMS OF DEPENDENCE

The identification of the involvement of the dopaminergic systems represents a considerable advance in our understanding of the dependence effects. Amongst other mechanisms it is now suggested that dopamine may be involved as a final neuromodulator after prior intervention of GABAergic and glutamatergic effector neurones.

The expert group recommends that the action of nicotine on neuromodulation mechanisms (dopamine, noradrenalin, serotonin) and neuroendocrine mechanisms (steroid and thyroid hormones) be studied in depth.

TO DESIGN STUDIES ON THE INFLUENCE OF REPEATED EXPOSURE TO NICOTINE ON CEREBRAL STRUCTURES AND THEIR FUNCTIONING DURING DEVELOPMENT AND IN ADULTHOOD

It has been shown in animal models that repeated administration of nicotine changes the morphology of neurones located in the regions involved in the reinforcing properties of drugs, and that this contributes to changes in their functional properties.

When exposure occurs during the prenatal period, sustained changes in the organisation of specific cerebral networks may lead to cognitive deficits in adulthood. The contribution of these changes to the pathophysiology of substance use still remains to be elucidated. The expert group recommends that animal models which are closer to human consumption (quantity, chronicity etc.) be developed and that the influence of chronic administration of nicotine during development and in adulthood on the organisation of the brain and its methods of communication be researched.

Studies on the effects of nicotine and tobacco on cognitive functions in human beings are still very controversial and some contain methodological bias. Cognitive effects are nevertheless of interest as these may be reinforcers of smoking behaviour. The expert group recommends that research be conducted into the cognitive effects of nicotine and possibly of other components of tobacco smoke, using double blind trials with measurements of plasma nicotine concentrations, compared to a placebo, and including non-abstinent and abstinent smokers, non-smokers, ex-smokers and occasional smokers. It would appear necessary to test the effects over a large range of cognitive tasks.

TO STUDY THE ROLE OF NON-NICOTINE COMPONENTS AND ADDITIVES IN DEPENDENCE

Tobacco smoke contains beta-carbolines such as harmane and norharmane, which have monoamine oxidase (MAO) inhibitory properties. The cerebral action of nicotine is maintained by different neuromodulators such as dopamine, which are normally degraded by these enzymes. Inhibition of these enzymes could therefore play a role in tobacco dependence. Because they potentiate the action of these neuromodulators by preventing their removal, the MAOI to which smokers are exposed is believed to result in long term maintenance of a high cerebral response to nicotine. The expert group recommends that the interactions between nicotine and other substances in tobacco (including certain additives) in the neuromodulation mechanisms be better understood. Components of tobacco smoke (acetaldehyde, beta-carbolines etc.) may also have effects on cognitive functions which may be involved in the dependence and may interfere with successful cessation.

TO IMPROVE UNDERSTANDING OF THE RISK FACTORS FOR TOBACCO DEPENDENCE AND TAKE INTO ACCOUNT OF THE EXISTENCE OF CRITICAL EXPOSURE PERIODS (FOETUS, INFANT, ADOLESCENT)

Not all individuals exposed to smoking at one time or another will necessarily become dependent and it is important to be able to identify specific dimensions of personality or

specific situations which the person will have to manage (notably stressful events) which are likely to emerge as risk factors for use and dependence, and which may have variable impact during the person's life. To this effect, the expert group recommends that longitudinal epidemiological studies be conducted in France on young people from the general population in order to identify the factors most associated with regular use of tobacco, the development of dependence and the ability to stop tobacco use.

In addition, a few epidemiological studies suggest that use of tobacco or even dependence (one single study) is greater in children or adolescents after high in utero exposure. The expert group recommends that the existing epidemiological studies which allow the impact of prenatal and neonatal exposure to tobacco on the risk of subsequent dependence be identified and exploited and that ongoing cohort studies be supported.

TO DEVELOP STUDIES ALLOWING THE GENES POTENTIALLY INVOLVED IN DEPENDENCE AND GENE-ENVIRONMENT INTERACTIONS TO BE IDENTIFIED

The involvement of genetic factors in dependence is now well accepted, although few genes have been identified to date. Studies are being directed towards the research into variants of genes involved in the metabolism of addictive substances in tobacco, primarily nicotine, and towards genes involved in the mechanism of action of nicotine and those involved in the regulation of dopaminergic, serotonergic or noradrenergic pathways.

The goal is to identify the assortments of gene variants, environmental factors and their interactions. Although the contribution of the genes implicated is relatively small (ranging in general from 0.4 to 2%) the interactions between certain genes or vulnerability to certain factors may considerably increase a person's risk (multiplying it by 10 to 40 times). The expert group recommends that the components of tobacco dependence which are genetically determined be identified, that research be conducted to explore the nature of gene-gene and gene-environment interactions and that research into genetic differences related to dependence between men and women or differences by age be increased.

Identification of the genes involved in tobacco dependence should be continued, with research into underlying biological mechanisms, i.e. whether these act directly by changing or stimulating the pharmacokinetics or pharmacodynamics of nicotine (and other substances in tobacco) and whether they interfere with personality traits or depressive state. These may not be specific to the actions of nicotine and may involve other substances in tobacco and may possibly coupled with other types of drug dependences. Finally it appears important to take into account the balance between harmful and protective genes to estimate the risk of dependence.

Knowledge of genetic influences could radically change the manner of treating or preventing tobacco dependence: identifying children at high risk, improving planning for cessation and sustainable abstinence, offering more effective strategies to relief patients of withdrawal symptoms; first line prescribing of the best pharmacological and/or psychological approach to help smokers with co-morbidities.

TO IDENTIFY THE ROLE OF THE SENSORY EFFECTS OF TOBACCO IN TOBACCO DEPENDENCE AND THEIR PART IN THE EFFICACY OF SOME NICOTINE REPLACEMENT THERAPIES

All sensory stimuli may contribute to the conditioned reinforcement of the smoker and, associated with a repetitive compulsive behaviour, may establish positive reinforcing circuits

and therefore contribute to maintaining tobacco dependence. The expert group recommends that research be conducted to establish whether the sensory effects perpetuate consumption, whether tolerance or sensitisation to the peripheral sensory effects of cigarettes develops over time and to assess the contribution of the peripheral sensory effects to the urge to smoke and craving for tobacco after stopping cigarettes.

Substances other than nicotine contained in tobacco smoke may contribute to the peripheral sensory effects of tobacco. It would therefore be interesting to determine whether smoke-free tobacco has sensory properties. Finally we might wonder whether we could increase the efficacy of nicotine replacement therapies by acting on the peripheral sensory effects of buccally absorbed nicotine.